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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/776,191	02/02/2001	Edwin L. Madison	24745-1607	3237

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EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/776,191	MADISON ET AL.	
	Examiner	Art Unit	
	Yong D Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *11 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,16-20,34-36,40-46,48-57,72-75,91,108,109,113-116,118-120 & 122-129* is/are pending in the application.

4a) Of the above claim(s) *10, 43-46, 48-57, 72-75, 91, 108-109, 113-116, 118-120 & 122-129* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-14,16-20,34-36 and 40-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *see attached*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a CIP of 09/657,986, now issued as U.S. Patent No. 6,797,504.

The amendment filed on August 11, 2004, amending claims 34, 40-46, 48-57, 72-75, 91, 108-109, 113-116, 118-120 and 122-129 and canceling claims 15, 21-33, 37-39, 47, 58-71, 76-90, 92-107, 110-112, 117, 121 and 130-136, has been entered.

Claims 1-14, 16-20, 34-36, 40-46, 48-57, 72-75, 91, 108-109, 113-116, 118-120 and 122-129 are pending.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-14, 16-20, 34-36, 40-42, 56-57, 72-75, 91, 108-109, 113-114 and 127-129) with an election of MTSP1 polypeptide in the reply filed on August 11, 2004 is acknowledged. The traversal is on the ground(s) that claim 1 of group I is a generic claim linking species of MTSP1 (claims 11-14, 16-20, 34-36 and 40-42), MTSP3 (claims 11-14, 16-20, 40-42 and 56-57), MTSP4 (claims 11-14, 16-20, 40-42 and 72-75), MTSP6 (claims 11-14, 16-20, 40-42, 91-114 and 127-129). This is found persuasive and if claim 1 is found to be allowable, the restriction requirement will be withdrawn and all claims directed to non-elected MTSP polypeptides that depends from the linking claims will be rejoined.

Applicants also traverse on the grounds that the restriction between the MTSP polypeptides is not consistent with the rules set forth in MPEP 803.04. This is not found persuasive because MPEP 803.04 relates to nucleotide sequences. The present claims

are drawn to polypeptides. Also, even though applicants are allowed up to ten nucleotide sequences, the notice in the 1192 O.G. 68 does not guarantee an applicant to more than one sequence.

The requirement is still deemed proper and is therefore made FINAL.

Claims 10, 43-46, 48-57, 72-75, 91, 108-109, 113-116, 118-120 and 122-129 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on August 11, 2004.

Notice of Possible Rejoinder: The Examiner notes that if claim1 is found directed to an allowable product, then claims 43-46, 48-55 and 115-126, which are directed to the process of making or using the patentable product, respectively, previously withdrawn from consideration as a result of a restriction requirement, would then be rejoined pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86; see also MPEP 821.04, *In re Ochiai,* and *In re Brouwer*). Since process claims 43-46, 48-55 and 115-126 would be rejoined and fully examined for patentability under 37 CFR 1.104 upon allowance of claim 1, applicants are instructed to amend said claims as deemed necessary according to rejections made against the elected claims.

Sequence Compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. It is particularly noted that the sequences in Figure 4 lack sequence identification numbers. See particularly 37 CFR 1.821(d).

Specification

Examiner notes that applicants have not updated the relationship of the instant application to its parent application (09/657,986) that has matured into a US patent (U.S. Patent No. 6,797,504). Examiner urges applicants to amend said information by providing the US patent number in response to this Office action.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 8/6/2001, 9/7/2001, 1/10/2002, 10/07/2002, 2/7/2003, 4/28/2003, 8/25/2003, 9/11/2003, 1/15/2004, 7/1/2004 and 9/8/2004 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional applications upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims11-14 and 34 of this application.

Provisional applications 60/179,982, 60/183,542, 60/213,124, 60/220,970 and 60/234,840 fail to provide adequate support for polypeptides comprising the serine protease domain of MTSP1. Provisional applications 60/179,982 and 60/183,542 describe polypeptides related MTSP3 and provisional application 60/213,124, 60/220,970 and 60/234,840 describe polypeptides related to MTSP4.

Therefore, the effective filing date for purpose of prior art is the filing date of 09/657,986, which is 9/8/2000.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Claim Objections

Claims 11-14 and 34 are objected for being drawn to non-elected subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 4 is directed to a polypeptide comprising protease domain of a human protein. Claim 4 is rejected under this section of 35 U.S.C. 112 because the claims are directed to a genus of polypeptides including natural, recombinant and modified polypeptide sequences whose structure has not been disclosed in the specification.

In the specification, a single human polypeptide is described as amino acids 615-855 of SEQ ID NO:2, representing the serine protease domain, having proteolytic activity. This description also adequately describes a genus, within the sequence limitation of the instant claim, of polypeptides having this particular function. Those sequences that are "human" are subset of this genus of polypeptides having proteolytic activity. The specification fails to define those structural features of SEQ ID NO:2 that are commonly possessed by members of the genus that distinguish them from other "non-human" polypeptides. Thus, one skilled in the art cannot visualize or recognize the identity of the members of the genus. As such, this single representative species does not adequately describe this subset according to its structure so that one of skill in the art can visualize and distinguish those amino acid sequences that are human, particularly in view of the large genus that includes both human and non-human sequences. Therefore, the instant claims are not adequately described.

Claims 1-9, 11, 16-20, 34-36 and 40-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-9, 11, 16-20, 34-36 and 40-42 are drawn to a polypeptide comprising a protease or catalytically active portion of type-II membrane-type serine protease (MTSP) from any source. Claims 11 and 34 limit the MTSP polypeptide to a MTSP 1 polypeptide from any source. Therefore, these claims are drawn to a genus of polypeptides having any structure. The specification only teaches one species, the polypeptide having the amino acid sequence of SEQ ID NO:50, corresponding to amino acids 615-855 of SEQ ID NO:2. One species is not enough to describe the whole genus and there is no evidence on the record of the relationship between the structure of the serine protease domain of SEQ ID NO:50 and the structure of the serine protease domain of any MTSP polypeptides. Further, the specification does not describe the structure of a catalytically active portion of a MTSP polypeptide. Therefore, the specification fails to describe a representative species of the genus of polypeptides comprising of a serine protease domain or a catalytically active portion of a MTSP polypeptide.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 1-9, 11, 16-20, 34-36 and 40-42.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-9, 11, 13-14, 16-20, 34-36 and 40-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide comprising amino acids 615-855 of SEQ ID NO:2 or the polypeptide of SEQ ID NO:50, does not reasonably provide enablement for a polypeptide comprising any protease domain of any type II membrane type serine protease or a catalytically active portion thereof, said polypeptide having a modification of 90-95% and mutants of said polypeptide having free Cysteine residues replaced with serine residues or a polypeptide comprising a serine protease domain having 40-95% sequence identity to amino acids 615-855 of SEQ DI NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 1-9, 11, 34-36 and 40-42 are drawn to polypeptides comprising a catalytically active domain of a MTSP/MTSP1 polypeptide. Claims 13-14 are drawn to a polypeptide comprising a serine protease domain having 40-95% sequence identity to amino acids 615-855 of SEQ DI NO:2. Claims 16-18 are drawn to polypeptides comprising protease catalytically active domains of a MTSP polypeptide wherein 90-95% of the amino acids are replaced. Claims 19-20 are drawn to polypeptides comprising protease catalytically active domains of a MTSP polypeptide wherein any free Cys residues are replaced with a Ser residue. Therefore, these claims are drawn to a genus of polypeptides having undefined structure.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides comprising a protease or catalytically active domain broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the polypeptide comprising amino acids 615-855 of SEQ ID NO:2, or the amino acids of SEQ ID NO:50.

It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides. The specification is limited to teaching the use of polypeptide

comprising amino acids 615-855 of SEQ ID NO:2 or the amino acids of SEQ ID NO:50 but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by the claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and variants of a protease or catalytically active domain or modifications of amino acids 615-855 of SEQ ID NO:2 because the specification does not establish: (A) regions of the protein structure which may be modified without affecting MTSP/serine protease activity; (B) the general tolerance of MTSP to modification and extent of such tolerance; (C) a rational and predictable scheme for

modifying any amino acid residue (up to 95% of the amino acids) with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including protease or catalytically active domains of MTSP with an enormous number of amino acid modifications of the MTSP polypeptides and of amino acids 615-855 of SEQ ID NO:2. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the serine protease domain or the catalytically active domain of MTSP having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and claims 2-9, 11-14, 16-20, 34-36 and 40-42 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to

particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite because it is unclear whether the protease domain has any catalytic activity.

Claims 2-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-3 are indefinite because the claims recite negative limitations. It is not clear as to how one skilled in the art can readily determine such limitations associated with the purified polypeptide.

Claims 6-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6-9 are indefinite because it is not clear as to how those skilled in the art will be readily able to identify the characteristics claimed to be associated with the claimed polypeptides.

Claim 35 and claim 36 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite because it is not clear whether the conjugate have the same activity of the polypeptide as it was before conjugation.

Claim 40 and claims 41-42 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the claims, the phrase "two or more polypeptides" is indefinite. It is not clear as to what type of polypeptides are encompassed by the above phrase. It is unclear whether the solid support comprises of different MTSP polypeptides, each having its own protease domain, or if the solid support comprises of same MTSP polypeptides having different protease domains. This is because claim 40 is limited to the polypeptides of claim 1.

Claim 42 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 42, the phrase "plurality of different MTSP protease domains" is indefinite. It is not clear as to what type of polypeptides are encompassed by the above phrase. It is unclear whether the solid support comprises of different MTSP polypeptides, each having its own protease domain, or if the solid support comprises of same MTSP polypeptides, having different protease domains. This is because claim 40 in which claim 42 deepens from is limited to the polypeptides of claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-9 and 34-36 and 40-41 are rejected under 35 U.S.C. 102(a) as being anticipated by Takeuchi et al.

Claims 1-9 and 34 are drawn to a polypeptide comprising a serine protease domain of MTSP having the characteristics recited in the claims. Claims 35-36 are drawn to a conjugate comprising a polypeptide comprising a serine protease domain of MTSP and a targeting agent. Claims 40 and 41 are drawn to a solid support comprising a polypeptide comprising a serine protease domain of MTSP.

Takeuchi et al. (Reference IJ : PTO-1449) teaches a polypeptide consisting of a serine protease domain that is 100% identical to amino acids 615-855 of SEQ ID NO:2 of the instant invention (page 11060, 2nd full paragraph). The MTSP of Takeuchi et al. is not expressed on normal endothelia cells (page 11054, last paragraph and page

11055, 2nd full paragraph), is of human origin (Figure 1), consists essentially of the protease domain having catalytic activity (page 11060, 2nd full paragraph), and is expressed in tumor cells (page 11055, top paragraph).

Takeuchi et al. teaches a catalytically active polypeptide comprising the serine protease domain linked to a His-tag (page 11055, 3rd full paragraph, page 11057, 4th full paragraph). Takeuchi et al. also teaches a solid support comprising said polypeptide (page 11057, 4th full paragraph and Figure 5). Therefore, the teaching of Takeuchi et al. anticipates claims 1-9 and 34-36 and 40-41.

Examiner notes that the contents of the reference were made public at the National Academy of Sciences colloquium held February 20-21, 1999 (see top of reference).

Claims 11-14 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Takeuchi et al.

Claims 11-14 and 34 are drawn to a polypeptide having a protease domain comprising of amino acids 615-855 of SEQ ID NO:2, a serine protease domain having at least 40-95% homology to the amino acids 615-855 of SEQ ID NO:2, or a protease domain encoded by a polynucleotide that hybridizes to SEQ ID NO:1.

Takeuchi et al. (Reference IJ : PTO-1449) teaches a polypeptide consisting of a serine protease domain that is 100% identical to amino acids 615-855 of SEQ ID NO:2 of the instant invention (page 11060, 2nd full paragraph). The serine protease domain is

encoded by a polynucleotide which hybridizes to SEQ ID NO:1 of the instant invention since the serine protease domain is identical to the serine protease domain of the instant invention. Therefore, the teaching of Takeuchi et al. anticipates claims 11-14 and 34.

Examiner notes that the contents of the reference were made public at the National Academy of Sciences colloquium held February 20-21, 1999 (see top of reference).

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a), which forms the basis for all obviousness rejections, set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9, 11-14 and 34 rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over O'Brien et al.

Claims 1-9, 11 and 34 are drawn to a polypeptide comprising a serine protease domain of MTSP.

O'Brien et al. (U.S. Patent No. 5,972,616 – reference P- PTO 1449) teaches a polypeptide having 100% identity to the full length MTSP1 of SEQ ID NO:2 of the instant invention (SEQ ID NO:2, columns 19-24). The properties recited in claims 2-3 and 6-9 are inherent properties of MTSP1 taught by O'Brien et al. since the polypeptide of O'Brien et al. and the instant invention have identical structure and therefore identical properties.

O'Brien et al. teaches a serine protease domain having proteolytic activity that is 100% identical to amino acids 615-855 of SEQ ID NO:2 (Figure 2, Figure 10 and SEQ ID NO:14). Although the protease domain of O'Brien et al. identified by SEQ ID NO:14 has not been purified, the protease domain in the reference and the polypeptide claimed by the applicants are one and the same. Therefore, the protease domain anticipates the instant invention.

Since the Office does not have facilities for examining and comparing applicant's polypeptide with the polypeptide of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the polypeptide of the prior art does not possess the same material structure and functional characteristics of the claimed polypeptide). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Figzgerald* et al., 205 USPQ 594.

O'Brien et al. teaches a method of expressing polypeptides via a vector in host cells. O'Brien et al. also teaches that the protease domain could be released the used

as a diagnostic which has the potential for a target for therapeutic intervention (Column 15, lines 35-38). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to express the protease domain of SQ ID NO:14 and purify the polypeptide. The motivation of making such a polypeptides is to use it as a diagnostic which has the potential for a target for therapeutic intervention. One of ordinary skill in the art would have had a reasonable expectation of success since expression of a heterologous polypeptide is routine in the art and O'Brien et al. teaches how to express heterologous polypeptides.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 35-36 and 40-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Brien et al.

Claims 35-36 are drawn to a conjugate comprising a polypeptide comprising a serine protease domain of MTSP and a targeting agent. Claims 40 and 41 are drawn to a solid support comprising a polypeptide comprising a serine protease domain of MTSP.

O'Brien et al. (U.S. Patent No. 5,972,616 – reference P- PTO 1449) teaches a polypeptide having 100% identity to the full length MTSP1 of SEQ ID NO:2 of the instant invention, as discussed above. O'Brien et al. also teaches that the protease domain could be released the used as a diagnostic which has the potential for a target for therapeutic intervention (Column 15, lines 35-38).

O'Brien et al. also teaches method of making fragments of SEQ ID NO:2 (Column 9, lines 22-55). O'Brien et al. teaches said fragments linked to another, polypeptide (Column 9, lines 54-55) and conjugated to bridging molecules (Column 6, lines 27-39) for detecting the polypeptide. Assays using polypeptides linked to the molecules taught by O'Brien et al. utilize solid supports.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a polypeptide comprising of the

serine protease domain of SEQ ID NO:2 taught by O'Brien et al. and to make conjugates and solid support comprising of a polypeptide comprised of the serine protease domain of SEQ ID NO:2. The motivation of making such a polypeptides is to use it as a diagnostic which has the potential for a target for therapeutic intervention. The motivation of making conjugates and solid supports comprising of said polypeptide is to use the conjugate and solid support in a variety of diagnostic assays. One of ordinary skill in the art would have had a reasonable expectation of success making fragments of a polypeptide is routine in the art and O'Brien et al. teaches how to make fragments of SEQ ID NO:2. One of ordinary skill in the art would have had a reasonable expectation of success in diagnostic assays using conjugates and solid supports comprising a polypeptide is very well known, as taught by O'Brien et al.

Claims 1 and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Brien et al. and Estell et al. in view of Takeuchi et al.

Claims 1 and 16-20 are drawn to a polypeptide comprising the serine protease domain of a MTSP wherein free Cys residues are substituted with Ser residues and a polypeptide having up to 90-95% modifications of the serine protease domain.

O'Brien et al. teaches a serine protease domain of a MTSP polypeptide, as discussed above.

The reference of O'Brien et al. does not teach a serine protease domain of a MTPSP polypeptides wherein free Cys residues have been replaced with Ser residues.

It is well known in the art that proteins form disulfide bonds via the SH groups of Cys residues. Upon making a polypeptide comprising a serine protease domain, a Cys residue which normally forms disulfide bonds in the full length polypeptide may be left free. For example, Takeuchi et al. (Reference IJ : PTO-1449) teaches that Cysteine at position 731 of SEQ ID NO:2 normally forms a disulfide bond with a Cys residue in the pro-protease domain (see page 11060, top left paragraph and Figures 1 and 2).

Cys residues are sensitive to oxidation due to their SH side group. Estell et al. (U.S. Patent No. 5,346,823) teaches that Cys residues replaced with Ser residues to decrease a polypeptide's susceptibility to oxidation (Abstract and Column 10, lines 34-38). Ser residues have similar side chains as Cys residues and substitution of a Cys residue with a Ser residue is a conservative substitution.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to replace free Cys residues in the protease domain taught by O'Brien et al. with a Ser residue. One of ordinary skill in the art would be motivated to make such a change in order to enhance stability of the polypeptide. One of ordinary skill in the art would have had a reasonable expectation of success since Estell et al. teaches successful decrease of a protein's susceptibility to oxidation by substituting residues sensitive to oxidation with conservative substitutions.

Therefore, the above references render claims 1 and 16-20 prima facie obvious to one of ordinary skill in the art.

None of the claims are in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

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Patent Examiner